Corticosteroids for Recurrent Pericarditis
High Versus Low Doses: A Nonrandomized Observation

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Background—Corticosteroid use is widespread in recurrent pericarditis, even if rarely indicated, and high doses (eg, prednisone 1.0 to 1.5 mg · kg^{-1} · d^{-1}) are generally recommended, although only weak evidence supports their use with possible severe side effects. The aim of this work was to compare side effects, recurrences and other complications, and hospitalizations of a low- versus high-dose regimen of prednisone for recurrent pericarditis.

Methods and Results—A retrospective review of all cases of recurrent pericarditis treated with corticosteroids according to different regimens from January 1996 to June 2004 was performed in 2 Italian referral centers. One hundred patients with recurrent pericarditis (mean age, 50.1±15.8 years; 57 females) were included in the study; 49 patients (mean age, 47.5±16.0; 25 females) were treated with low doses of prednisone (0.2 to 0.5 mg · kg^{-1} · d^{-1}), and 51 patients (mean age, 52.6±15.3; 32 females) were treated with prednisone 1.0 mg · kg^{-1} · d^{-1}. Baseline demographic and clinical characteristics were well balanced across the groups. Each initial dose was maintained for 4 weeks and then slowly tapered. After adjustment for potential confounders (age, female gender, nonidiopathic origin), only high doses of prednisone were associated with severe side effects, recurrences, and hospitalizations (hazard ratio, 3.61; 95% confidence interval, 1.96 to 6.63; $P<0.001$).

Conclusions—Use of higher doses of prednisone (1.0 mg · kg^{-1} · d^{-1}) for recurrent pericarditis is associated with more side effects, recurrences, and hospitalizations. Lower doses of prednisone should be considered when corticosteroids are needed to treat pericarditis. **(*Circulation*. 2008;118:667-671.)**

Key Words: corticosteroids ■ pericarditis ■ pericardium ■ therapy

Even if rarely indicated, recurrent pericarditis often is treated with corticosteroids in clinical practice. Corticosteroids can induce a quick response with symptom control and initial remission. Despite the fact that guidelines and reviews[1–9] recommend limiting the use of corticosteroids in pericarditis, the use of these drugs is widespread. Only 1 retrospective study supports their use.[10] Following this study, reviews and current European guidelines on the management of pericardial diseases[3,5–8] have recommended the use of high doses of prednisone (1.0 to 1.5 mg · kg^{-1} · d^{-1}) for 1 month in patients with recurrent pericarditis when corticosteroids are considered.

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Unfortunately, the treatment often is quickly tapered because of the fear of possible side effects, and relapses and severe side effects related to the need of prolonged treatments with steroids are common. Thus, one of the most troublesome issues in pericardial diseases is how to manage a patient with recurrent pericarditis and corticosteroid dependence.[1–10] When high doses are considered, side effects are not uncommon and may be cause of early withdrawal of the drugs. Low to moderate doses of corticosteroids (ie, prednisone 0.2 to 0.5 mg · kg^{-1} · d^{-1}) are commonly prescribed to treat serositis in patients with rheumatologic conditions. Use of these lower doses may be a way to minimize side effects.

The aim of the present study was to retrospectively compare the side effects, recurrences and other complications, and hospitalizations of 2 different therapeutic regimens of corticosteroids for recurrent pericarditis: high doses (ie, prednisone 1.0 mg · kg^{-1} · d^{-1}) and low doses (ie, prednisone 0.2 to 0.5 mg · kg^{-1} · d^{-1}).

Methods

Study Design and Subjects

Data prospectively recorded from all clinical cases of recurrent pericarditis treated with corticosteroids from January 1996 to June

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Table 1. Tapering Regimen of Prednisone in Recurrent Pericarditis

Prednisone Daily Dose, mg	Tapering
>50	10 mg/d every 1 to 2 wk
50–25	5–10 mg/d every 1 to 2 wk
25–15	2.5 mg/d every 2 to 4 wk
<15	1.25 to 2.5 mg/d every 2 to 6 wk

Every decrease in prednisone dose should be done only if the patient is asymptomatic and C-reactive protein is normal, particularly for doses <25 mg/d.

2004 in 2 Italian referral centers for the treatment of pericarditis (center A, Maria Vittoria Hospital, Torino; center B, Niguarda Hospital, Milano) were retrospectively reviewed. Inclusion criteria were definite diagnosis of recurrent pericarditis (idiopathic, viral, and autoimmune causes, including postpericardiotomy syndromes, and connective tissue diseases) and age ≥18 years. Exclusion criteria were tuberculous and neoplastic or purulent origins. The clinical diagnosis of recurrence was based at least on recurrent chest pain and ≥1 of the following signs: fever, pericardial friction rub, ECG changes, or echocardiographic evidence of new or worsening pericardial effusion. Elevation of C-reactive protein or increased erythrocyte sedimentation rate was required in all cases to confirm the diagnosis of recurrence.[11–15]

Treatment Plan

In both institutions, corticosteroid therapy was prescribed only in patients with aspirin and nonsteroidal antiinflammatory drug (NSAID) contraindications, intolerance, or failure. The corticosteroid of choice was prednisone. Two different doses were prescribed for 4 weeks and then gradually tapered: high doses ($1.0\ mg \cdot kg^{-1} \cdot d^{-1}$)[10] in center A or low doses (0.2 to $0.5\ mg \cdot kg^{-1} \cdot d^{-1}$) in center B, according to local treatment protocols. Tapering was similar in the 2 regimens; a detailed description of the tapering according to prednisone daily doses is reported in Table 1. Each decrement was attempted in the absence of symptoms and when C-reactive protein levels were normal. If symptoms recurred during tapering, every effort was made not to increase the dose of or to reinstitute corticosteroids and to control symptoms by beginning or increasing the doses of aspirin or NSAID. Because these are tertiary referral centers, most patients were referred after failure of previous therapies, including steroids, and in these cases, the dose and type of corticosteroid were modified according to the described protocol. During tapering, aspirin or an NSAID was added whenever possible using a gastroduodenal prophylaxis with a proton-pump inhibitor as previously published,[8,11] and colchicine (0.5 to 1.0 mg/d) was added if tolerated. After routine care of recurrent pericarditis in the 2 centers, all patients had a clinical and echocardiographic follow-up at least up to 18 months after the initial diagnosis of recurrence.

Outcomes

The primary outcome was the rate of severe side effects. A severe adverse event was considered an untoward event that was fatal or life-threatening, required hospitalization, or was significantly or permanently disabling or medically significant (may jeopardize the patient and may require medical or surgical intervention to prevent an adverse outcome). Secondary outcomes of the study were the recurrence rate, cardiac tamponade, constrictive pericarditis, minor side effects, and hospitalization related to recurrent pericarditis.

Patients were considered to be in remission when they were symptom free with no clinical, ECG, or echocardiographic signs and with normalization of C-reactive protein.[11–14]

Statistical Analysis

Data are expressed as mean±SD. Comparison between patient groups was performed with an unpaired *t* test for continuous variables; Fisher exact test was used for proportions between groups. A value of $P<0.05$ was considered statistically significant.

Table 2. Baseline Clinical Characteristics of the Studied Population

Feature	Group 1, Low Dose (n=49)	Group 2, High Dose (n=51)	*P*
Age, y	47.5±16.0	52.6±15.3	0.106
Women, n (%)	25 (51.0)	32 (62.7)	0.313
Pericardial effusion, n (%)	14 (28.6)	17 (33.3)	0.669
Cardiac tamponade, n (%)	3 (6.1)	1 (2.0)	0.357
Idiopathic origin, n (%)	35 (71.4)	38 (74.5)	0.823
Autoimmune origins, n (%)*	14 (28.6)	13 (25.5)	0.823
Mean recurrences, n	4.9±6.9	5.1±3.2	0.773

Values are mean±SD when appropriate. Prednisone low dose was 0.2 to 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ and high dose was 1.0 to 1.5 $mg \cdot kg^{-1} \cdot d^{-1}$. The mean number of recurrences is reported at the beginning of the observation.

*Autoimmune causes include connective tissue diseases and postpericardiotomy syndromes.

Time-to-event distributions were estimated with the Kaplan-Meier method and compared by use of the log-rank test. The Cox proportional-hazards model was used to adjust for age and other potential confounders at baseline, including female gender and nonidiopathic origin. All analyses were performed with the SPSS 13.0 software package (SPSS Inc, Chicago, Ill).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

One hundred consecutive patients with recurrent pericarditis (mean age, 50.1±15.8 years; 57 women) who were treated with corticosteroids from January 1996 to June 2004 were included in this retrospective study. Information on vital status and clinical follow-up data were available in all patients for a mean follow-up of 55.8 months (range, 18 to 96 months). Forty-nine patients (mean age, 47.5±16.0; 25 women) were treated with lower doses of prednisone (0.2 to $0.5\ mg \cdot kg^{-1} \cdot d^{-1}$; group 1), and 51 patients (mean age, 52.6±15.3; 32 females) were treated with prednisone $1\ mg \cdot kg^{-1} \cdot d^{-1}$; group 2). Baseline demographic and clinical characteristics were well balanced across the groups (Table 2).

Outcomes

Patients treated with high doses of prednisone (group 2) had a higher rate of severe side effects compared with patients treated with lower doses (group 1) (23.5% versus 2.0%, respectively; $P=0.002$).

Recorded severe side effects included vertebral collapse in 4 cases, severe osteoporosis requiring medical intervention in 4 cases, and severe cushingoid syndrome in 5 other cases.

A higher recurrence rate was recorded in group 2 than in group 1 (64.7% versus 32.6%, respectively; $P=0.002$), as well as a higher frequency of minor side effects (including abdominal pain, dyspepsia, sodium-water retention, hyperglycemia, and skeletal myopathy) and disease-related hospitalizations (31.4% versus 8.2%; $P=0.005$). A detailed summary of the follow-up data is reported in Table 3.

After adjustment for potential confounders (age, female gender, nonidiopathic origin), only high doses of prednisone were associated with severe side effects, recurrences, and

Table 3. Follow-Up Data of the Studied Population

	Low Doses (n=49)	Prednisone 1 mg · kg^{-1} · d^{-1} (n=51)	*P*
Prednisone, mg*	33.3±12.6	68.8±9.6	<0.001
Colchicine, n (%)	40 (81.6)	41 (80.4)	0.920
Follow-up, mo	57.6±27.5	54.1±17.8	0.450
Severe side effects, n (%)	1 (2.0)	12 (23.5)	0.002
Minor side effects, n (%)	7 (14.3)	10 (19.6)	0.597
Recurrence, n (%)	16 (32.6)	33 (64.7)	0.002
Hospitalization, n (%)	4 (8.2)	16 (31.4)	0.005

Values are mean±SD when appropriate. No cases of cardiac tamponade and constriction were recorded in either group.

*Mean dose.

hospitalizations (hazard ratio, 3.61; 95% confidence interval, 1.96 to 6.63; $P<0.001$; Table 4).

Patients treated with prednisone 1 mg · kg^{-1} · d^{-1} had a lower event-free survival compared with those treated with lower doses (the Figure). Assessed adverse events included severe side effects, recurrences, cardiac tamponade, and constrictive pericarditis.

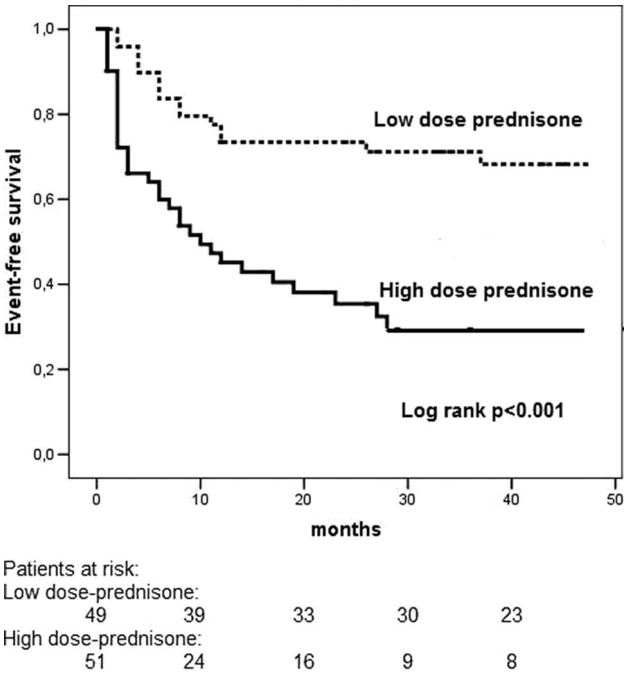

Figure. Event-free survival of patients treated with prednisone 1 mg · kg^{-1} · d^{-1} (thick line) vs those treated with lower doses (dotted line). Adverse events included severe side effects, recurrences, cardiac tamponade, and constrictive pericarditis.

Discussion

Major Findings

The present study challenges the current practice of using high doses of prednisone or other corticosteroids to treat pericarditis. Corticosteroid use should be restricted in pericarditis, but when indicated, high doses are recommended in reviews and the European guidelines on the management of pericardial diseases.[5–8] Although the practice of using high doses of prednisone is not uncommon and was the established regimen for decades, the evidence supporting this indication in recurrent pericarditis is weak, based only on a small retrospective study.[10] In this study, 12 patients with recurrent pericarditis unrelated to any systemic disease were treated with a 3-month course of high-dose prednisone (1.0 to 1.5 mg · kg^{-1} · d^{-1}) for 1 month and subsequent gradual tapering. When prednisone tapering was started, all patients received a 5-month course of aspirin (1.6 g/d until steroid withdrawal and then 0.8 g/d). During a mean follow-up of 42 months, treatment with high doses of prednisone resulted in stable remission in all except 1 patient. In this study, the efficacy of prolonged treatment with aspirin cannot be excluded as an explanation of the overall good remission rate. Moreover, 3 patients (25%) had severe steroid-related adverse effects; 2 of them were treated with other immunosuppressive treatments (1 with azathioprine, 1 with cyclophosphamide).

Table 4. Hazard Ratios for Severe Side Effects, Recurrences, or Hospitalizations in the Cox Proportional-Hazards Model

Feature	HR	95% CI	*P*
Age	0.98	0.97–1.01	0.130
Female gender	1.23	0.68–2.19	0.487
Nonidiopathic cause	1.40	0.77–2.54	0.267
High doses of prednisone	3.61	1.96–6.63	<0.001

HR indicates hazard ratio; CI, confidence interval.

Lower doses of steroids are commonly used to treat serositis in patients with chronic autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome.[15,16] These therapeutic schemes also might be reasonably applied in recurrent pericarditis.

In fact, corticosteroid toxicity is related to both the average dose and cumulative duration of treatment. For example, in a study on rheumatoid arthritis, the average daily prednisone dose was the strongest predictor of serious side effects related to steroid therapy (odds ratio, 4.5 for prednisone 5 to 10 mg but 32.3 for prednisone 10 to 15 mg). The correlation with side effects was either dose and time dependent even after correction for the severity of the disease.[17]

Guidelines recommend osteoporosis prevention when these drugs are used, an issue often forgotten in clinical practice. Supplementation with calcium and vitamin D (1500 mg/d and 800 IU/d, respectively) or an activated form of vitamin D (eg, alfacalcidol 1 μg/d or calcitriol 0.5 μg/d) should be offered to all patients receiving glucocorticoids to restore normal calcium balance. Moreover bisphosphonates are recommended to prevent bone loss in all men and postmenopausal women in whom long-term treatment with glucocorticoids is initiated at a ≥5-mg/d dose of prednisone or equivalent and in men and postmenopausal women receiving long-term glucocorticoids in whom the bone mineral density T score at either the lumbar spine or the hip is below normal.[18,19] On the contrary, proton-pump inhibitors are not routinely indicated when corticosteroids are used without NSAIDs.[20]

Moreover, corticosteroid therapy has been found to be an independent risk factor for recurrences not only in acute

pericarditis (odds ratio, 4.30)[13] but also for the first recurrence (odds ratio, 2.9 to 10.0)[12,14] and after multiple recurrences (odds ratio, 6.7).[21] A possible explanation is that some recurrences may be provoked by acute or chronic viral infections,[2,22] and corticosteroids could promote viral replication.[13,23]

Thus, NSAIDs should be the mainstay of therapy for acute and recurrent pericarditis, and corticosteroids should be considered only as a second-choice therapy in patients with poor general conditions or in frequent crisis unresponsive to NSAIDs as a last resort. In these cases, very low tapering only after stable remission with symptom resolution and normalization of C-reactive protein is the key to successful management of the disease, similar to what is often done in polymyalgia rheumatica. During tapering, colchicine should always be considered, starting with low doses (eg, 0.5 mg, to improve gastrointestinal tolerability).[13–15] Growing evidence shows that the drug may be effective in preventing recurrences, reducing the need for prolonged treatment with steroids.[14,15,21,23,24]

Intrapericardial administration of corticosteroids has been proposed as a means to minimize steroid-induced side effects,[25,26] but there are technical considerations that may limit the usefulness of intrapericardial therapy. If the patient has small or no pericardial effusion, pericardioscopy or the PerDUCER technique must be available to utilize this form of treatment, and both remain investigational tools for most.

The present study shows that the use of low to moderate doses of prednisone (0.2 to 0.5 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) is efficacious and may substantially reduce the risk of severe side effects that may be life-threatening and often cause the early withdrawal of therapy. Early withdrawal and quick tapering resulting from side effects are common causes of recrudescence of the disease, explaining a double recurrence rate in patients treated with high doses of prednisone (see Table 3). While awaiting future randomized controlled trials, we propose abandoning high-dose prednisone as an initial approach to recurrent pericarditis unresponsive to optimal NSAID and colchicine treatment.

Study Limitations

A first limitation of the study is the lack of a randomized design and the retrospective design. Nevertheless, the 2 centers used a standardized different protocol for prednisone. Moreover, a similar population was referred to the 2 centers, and the 2 study groups were well balanced for relevant clinical data such as origin, gender, and severity of the disease at baseline (number of previous recurrences, previous cardiac tamponade, pericardial effusion; see Table 2). We also performed an adjustment for more evident potential confounders (age, female gender, and nonidiopathic origin). Thus, we can reasonably exclude that more severe cases were assigned to a specific treatment such as high-dose prednisone while milder forms were assigned to low doses. A second limitation is that a definitive diagnosis based on cytology, immunohistochemistry, or pericardial, endomyocardial, or epicardial biopsy is not available in all cases. A complete diagnostic workup is clearly worthwhile and should be available if possible before any treatment, particularly when corticosteroids are adopted. In the ideal world, idiopathic pericarditis would not exist. In the real world, in some cases of acute or recurrent pericarditis, the cause has not been or cannot be established. Because of the complexity of establishing whether the relapse is an autoimmune effect or the result of reinfection or a new infection, many clinicians treat these patients empirically, and they often resort to corticosteroids.

Even with its limitations, our study challenges current practice that is based on only 1 study of 12 patients[10] and is associated with an unacceptably high rate of severe side effects. This study may serve as a basis for a future prospective randomized trial.

Conclusions

Corticosteroid therapy is a double-edged weapon in patients with pericardial diseases; it may have specific but rare indications (definite rheumatologic disease, presumed autoimmune origin, intolerance or contraindications to aspirin or NSAIDs, pregnancy), but it should be a last resort. High doses have been recommended with only a single small retrospective study supporting this use in recurrent pericarditis, whereas lower doses usually are used to treat pericarditis in autoimmune diseases. We observed that these doses (prednisone 0.2 to 0.5 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) were more effective than higher doses in reducing recurrences and hospitalizations and induced considerably fewer side effects, so we propose that these lower doses should be considered in clinical practice. When corticosteroids are used, osteoporosis prevention is recommended as a rule. It is anticipated that this change in clinical practice will greatly decrease the burden of corticosteroids side effects in pericarditis while maintaining efficacy.

Disclosures

None.

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CLINICAL PERSPECTIVE

The present observational study challenges the widespread practice of using high doses of prednisone or other corticosteroids to treat pericarditis. Use of corticosteroids should be restricted in pericarditis, but when indicated, high doses (prednisone 1.0 to 1.5 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) have been recommended in reviews and in the European guidelines on the management of pericardial diseases, although only a single small retrospective study supported high-dose use in recurrent pericarditis. Lower doses usually are used to treat pericarditis in autoimmune diseases. In this nonrandomized observation, it appeared that higher doses of prednisone (1.0 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}) for recurrent pericarditis were associated with more side effects, recurrences, and hospitalizations (hazard ratio, 3.61; 95% confidence interval, 1.96 to 6.63) than lower doses (prednisone 0.2 to 0.5 mg $\cdot$ kg^{-1} $\cdot$ d^{-1}). It is important to search for a cause of recurrent pericarditis as diligently as possible, with therapy directed at the specific cause. This observational study challenges the current practice of routine high-dose corticosteroids for recurrent "idiopathic" pericarditis and should serve as the basis for a randomized trial.